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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/374,586	08/13/99	PINSKY	D 59167/JPW/JM

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EXAMINER	
CHEN, S	
ART UNIT	**PAPER NUMBER**
1633	13

DATE MAILED: 02/28/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

13

Office Action Summary	Application No. 09/374,586	Applicant(s) PINSKY, DAVID J.	
	Examiner Shin-Lin Chen	Art Unit 1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 November 2000* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13 and 16-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13 and 16-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *11* .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

It should be noted that the examiner for this patent application has been changed. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9 am to 5:30 pm.

Applicants' amendment filed 11-27-00 has been entered. Claims 14 and 15 have been canceled. Claims 1, 17 and 25 have been amended. Claims 1-13 and 16-26 are pending.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-13, 16 and 26 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention and is repeated in the preceding Official action mailed 5-24-00 (Paper No. 8). Applicant's arguments filed 11-27-00 have been fully considered but they are not persuasive.

Applicants argue that a CD39 polypeptide is fully described and there is sufficient written description in the specification regarding the variants of soluble CD39, such as page 8, line 25-

35, pages 9-12, and the specification describes that the fragment or variants of soluble CD39 would have the ability to inhibit adenosine diphosphate-mediated platelet aggregation by increasing adenosine diphosphate catabolism. This is not found persuasive because the specification of the present application only provides a general disclosure on the composition of CD39 variants, such as they have conservative substitutions, deletions, or insertions which do not abolish the biological activity associated with CD39 and which may have increased potency, bioavailability, stability or decreased toxicity. The specification fails to indicate what distinguishing features of the active fragment of CD39 must exist for the utilization of said active fragment in the claimed invention. The structural features that could distinguish CD39 fragments in the genus from others in the protein class are missing from the disclosure. No common structural attributes identify the members of the genus. Thus, claims 1-13, 16 and 26 remain rejected under 35 U.S.C. 112 first paragraph for the reasons set forth above and the reasons set forth in the preceding Official action mailed 5-24-00 (Paper No. 8).

3. Claims 1-13 and 16-26 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic mouse comprising a homozygous deletion in CD39 and its use in identifying compounds which inhibit platelet aggregation via the ADP pathway; and the use of soluble CD39 in the treatment and prevention of thrombotic and ischemic disorders in mice and BIBU52 in rhesus and marmoset monkeys (Guth et al., abstract), does not reasonably provide enablement for the use of any CD39 fragment or full-length CD39 (SEQ ID No. 1) in treating or preventing stroke; or the use of an animal model in testing for

compounds which inhibit platelet aggregation via any pathway. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Applicants argue that working example of a particular claimed invention is not required for patentability and the specification provides extensive guidance for carrying out assays to analyze the function of the variants of soluble CD39. Applicants further argue that one of ordinary skill in the art would have routinely carried out platelet aggregation assay and/or in vivo assay to assess the ability of a candidate CD39 variant without undue experimentation. This is not found persuasive because it was known in the art that a single amino acid change could alter the function of a protein. The amino acid sequence of a protein determines its structural and functional properties (including half-life), and predictability of which amino acids can be modified within a protein's sequence and still result in similar activity or result in stabilization of the protein is extremely complex, and well outside the realm of routine experimentation, because accurate predictions of a protein's structure from mere sequence data are limited. It would be unpredictable whether a substitution, a deletion, or an insertion within the soluble CD39 protein sequence would still retain activity of the soluble CD39 in inhibiting adenosine diphosphate-mediated platelet aggregation by increasing adenosine diphosphate catabolism to a subject without increasing incidence of intracerebral hemorrhage. Thus, one skilled in the art would have had to engage in undue experimentation to practice the invention over the full scope claimed.

Applicants argue that successful treatment of a mouse model of a human disease has been well accepted by those skill in the art as being reasonably predictive of success in human therapy and the soluble CD39 has been shown to improve stoke outcome. This is not found persuasive because of the following reasons:

Firstly, as discussed above that protein structure or function is not predictable from mere protein sequence and one skilled in the art at the time of the invention would not be able to predict whether a substitution, a deletion, or an insertion within the soluble CD39 protein sequence would still retain the biological activity of the soluble CD39.

Secondly, as discussed in the preceding Official action mailed 5-24-00 (Paper No. 8) that it was known in the art at the time of the invention that proteins involved in thrombosis displayed different levels of activity between species. Such and the unpredictability of the biological function of the various variants of the soluble CD39 would require one skilled in the art at the time of the invention undue experimentation to practice over the full scope of the invention. Further, it was known in the art a success in the treatment of a mouse model could not be readily translated into a success in treating human disease because they differ in physical structure and in physiological environment.

Applicants argue that it would be considered a routine experimentation to optimize the dose of any particular chosen CD39 active variant and a considerable amount of experimentation is permissible, if it is merely routine, or if the specification provides a reasonable amount of

guidance. This is not found persuasive because of the reasons set forth above and the reasons set forth in the preceding Official action mailed 5-24-00 (Paper No. 8).

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 17 and 20-24 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Guth et al. (8/97) in view of Gayle et al. (1998) and Choudhri et al., 1998 (J. Clin. Invest. Vol. 102, No. 7, p. 1301-1310 IDS-exhibit 8). Applicants' amendment filed 11-27-00 necessitates this new ground of rejection.

Guth discloses the use of three different animal models of recurrent arterial thrombus formation to test the efficacy of a compound, e.g. BIBU52 to inhibit ADP driven platelet aggregation in rhesus and marmoset monkeys. Guth does not disclose the use of CD39 or the compound does not increase the incidence of intracerebral hemorrhage.

Gayle discloses a recombinant soluble form of CD39 and demonstrate its antithrombotic activity *in vitro* by catabolizing ADP and resulting in the inhibition of platelet aggregation, and that it remained biologically active in vivo while circulating for prolonged periods of time (e.g. abstract, Figure 1, p. 1858).

Choudhri discloses testing the effects of a potent antiplatelet agent given both before and after the onset of middle cerebral arterial (MCA) occlusion in a murine model of stroke and shows a novel inhibitor of the glycoprotein IIb/IIIa receptor (SDZ GPI 562) exhibits a dose-dependent reduction of cerebral infarct volumes as well as improvement in postishchemic cerebral blood flow. Choudhri also teaches GPI 562 causes a dose-dependent increase in tail vein bleeding time, but intracerebral hemorrhage (ICH) is not significantly increased at therapeutic doses (e.g. abstract).

It would have been obvious for one of ordinary skill in the art at the time of the invention to utilize an animal model of thrombosis to test for the effect of a potential therapeutic compound, such as soluble form of CD39 or GPI 562, on inhibiting ADP driven platelet aggregation and without increasing incidence of intracerebral hemorrhage.

One of ordinary skill at the time the invention was made would have been motivated to use the soluble CD39 as the test compound in the model set forth above because Gayle teaches it inhibits platelet aggregation *in vitro* by catabolizing ADP and that it remains biologically active *in vivo*, and Choudhri teaches antiplatelet agent, such as GPI 562, may cause increasing bleeding time in tail vein but ICH is not significantly increased at therapeutic doses, thus displaying the potential to inhibit platelet aggregation in an animal under thrombotic conditions and without increasing the incidence of ICH.

Applicants argue that both Guth and Gayle do not teach or suggest a method for determining whether a compound inhibits platelet aggregation and/or fibrin deposition by increasing ADP catabolism and does not increase ICH. This is not found persuasive because of the Choudhri reference and the reasons set forth above.

Applicants argue that both Guth and Gayle do not teach the screening method as claimed. This is not found persuasive because Gayle does teach comparison of platelet aggregation with and without the presence of soluble CD39 (e.g. p. 1853) and it was well known and would have been obvious for one of ordinary skill to compare the results of an animal model with and without the treatment of a test compound in order to determine the effects of said test compound.

6. Claims 25 and 26 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Guth et al. (8/97) in view of Gayle et al. (1998) and Choudhri et al., 1998 (J. Clin. Invest. Vol.

102, No. 7, p. 1301-1310, IDS-exhibit 8) as applied to claims 17 and 20-24 above, and further in view of Beaudoin et al., (US Patent No. 5,798,241).

The teachings of Guth, Gayle and Choudhri are as discussed above. Beaudoin teaches the use of a composition comprising mammalian ATP diphosphohydrolase with a pharmaceutically acceptable carrier to reduce platelet aggregation and thrombogenicity (claim 5, col. 9, lines 34-37).

It would have been obvious for one of ordinary skill in the art at the time of the invention to utilize a compound identified from an animal model of thrombosis which displays the activity of catabolizing ADP and without increasing incidence of intracerebral hemorrhage according to the collective teachings of Guth, Gayle and Choudhri, in a pharmaceutical composition as taught by Beaudoin in order to inhibit platelet aggregation in an animal under thrombotic conditions and without increasing the incidence of ICH.

Applicants argue that Guth, Gayle and Beaudoin do not teach or suggest a method for determining whether a compound inhibits platelet aggregation and/or fibrin deposition by increasing ADP catabolism and does not increase ICH. This is not found persuasive because of the Choudhri reference and the reasons set forth above.

Conclusion

No claim is allowed.

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MEP. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Clark can be reached on (703) 305-4051. The fax phone number for this group is (703) 308-4242.

Questions of formal matters can be directed to the patent analyst, Kimberly Davis, whose telephone number is (703) 305-3015.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.

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